

REMARKS

Claims 1-40 have been canceled. New Claims 41-87 have been added and are now active in this case.

REQUEST FOR RECONSIDERATION

Applicants wish to thank Examiner Hartley for the helpful and courteous discussion conducted with their U.S. representative on August 25, 2000. In accordance with the remarks made during the discussion, Applicants have amended the claims in order to clarify the present invention. Applicants now wish to make the following additional remarks.

Currently, in order to deliver drugs across the blood brain barrier of mammals, it has been deemed necessary to use nanoparticles to which drugs are complexed (incorporated or adsorbed) and which nanoparticles are surrounded by a coating made of an appropriate surfactant. See, for example, Kreuter (WO 95/22963), described at page 1 of the present specification. Quite surprisingly, it has now been discovered that effective nanosphere drug targeting systems can be provided, which do not require an outer coating of surfactant, and which can, therefore, be produced much more simply.

In particular, the present invention provides, in part, a drug targeting system for administration to a mammal, which contains:

a) nanoparticles made of a polymeric material, the nanoparticles being free of a surfactant surface coating and containing the polymeric material, one or more physiologically effective substances to be delivered to the mammal and one or more stabilizers for the nanoparticles allowing targeting of the physiologically effective substances to a specific site within or on a mammalian body;

wherein the stabilizers are selected from the group consisting of polysorbate 85,

polysorbate 81, dextran 12,000, carboxylic acid esters of glycerol, sorbitan monostearate, sorbitan monooleate, polyoxamer 188, polyoxamines, alkoxylated ethers, alkoxylated esters, alkoxylated mono-, di- and triglycerides, alkoxylated phenols and diphenols, substances of the Genapol<sup>R</sup> and Bauki<sup>R</sup> series, sodium stearate, metal salts of alcohol sulfates, metal salts of sulfosuccinates and mixtures of two or more of these substances; and

b) a physiologically acceptable carrier, which allows transport of the nanoparticles to the target within said mammal after administration.

Claims 1-29 and 31-40 stand rejected under 35 U.S.C. §102(b) as being anticipated by Kreuter (WO 95/22963), Canal (EP 486959), Dyatlov (WO 94/15590) or Hyon (EP 330180). However, none of these references, either alone or in combination, describes or suggests the present invention.

In particular, Kreuter et al, as noted at page 1 of the present specification, necessarily teach the use of a surfactant coating on the nanoparticles thereof. Quite clearly, the present invention avoids the use of the surfactant coating. In fact, one of the principle objects of the present invention is the avoidance of such a surfactant surface coating on the nanoparticles.

Notably, Kreuter et al describe the preparation of nanoparticles "in conventional ways". See the Abstract. The nanoparticles are "then coated with additional surfactant and given to the body of animals or humans". See the Abstract. Thus, the nanoparticles of this reference are clearly characterized by the presence of an outer coating of surfactant.

Moreover, the stated reason for using this outer coating of surfactant is to allow "drugs or diagnostic agents to cross the blood-brain barrier (bbb)". See the Abstract. Kreuter et al describe the many conventional approaches which have been used to allow administered drugs to cross the blood-brain barrier. See pages 2-5 thereof. In contrast thereto, Kreuter et al teach that their invention:

... is based on the surprising finding that treatment of nanoparticles having a drug absorbed, adsorbed or incorporated therein with a sufficient coating of an appropriate surfactant allows the adsorbed drug to traverse the bbb. See page 6 thereof.

Further, Kreuter et al teach that:

The critical, innovative step is that after drug absorption or incorporation, the nanoparticles are coated with surfactants by incubating them in a surfactant solution under appropriate conditions. The surfactant allows penetration of the bbb by the drug without physical modification of the nanoparticle or the drug itself. See page 7 thereof.

In contrast, the present invention surprisingly avoids the use of the outer coating of surfactant as taught by Kreuter et al. See pages 3 and 4 of the present specification. Clearly, in view of the teachings of Kreuter et al, one skilled in the art would have no motivation to avoid the use of the outer coating of surfactant, as without the coating, one skilled in the art would not expect administered drugs to cross the blood-brain barrier as in the present invention.

Furthermore, the particular stabilizers used in accordance with the present invention are readily distinguishable from the substances used in Dyatlov et al and Canal et al. Notably, the present invention uses specific stabilizers which are neither disclosed nor suggested by either of these cited references.

Further, the emulsifying agents of Hyon et al are merely used to stabilize the emulsion therein, which is either a O/O type emulsion or a W/O type emulsion. That is, Hyon et al clearly teach the use of any conventional emulsifying agent insofar as they are able to form a stable O/O or W/O type emulsion. Thus, the stabilizer of Hyon et al is a stabilizer of the emulsion and is clearly not incorporated into a nanoparticle. In contrast, the stabilizer of the present invention is incorporated into the polymer of the nanoparticle for

stabilization in order to obtain the desired targeting of the nanoparticles to or on specific targets in or on the mammalian body without using the outer surfactant coating of Kreuter et al.

Quite clearly, one skilled in the art would not be put in possession of the present invention even from the combined teachings of these references.

Hence, this ground of rejection is believed to be unsustainable and should be withdrawn.

Claims 1-20 and 31-40 stand rejected under 35 U.S.C. §103(a) as being unpatentable over any one of Kreuter et al, Canal, Dyatlov or Hyon et al. However, none of these references, either alone or in combination, describes or suggests the present invention.

Specifically, the remarks noted above are deemed to be applicable to this ground of rejection as well. Quite clearly, one skilled in the art would not be put in possession of the present invention even from the combined teachings of these references.

Hence, this ground of rejection is believed to be unsustainable and should be withdrawn.

Claim 30 stands objected to under 37 C.F.R. §1.75(c).

However, in view of the above amendments, this ground of rejection is believed to be moot.

Claims 31-37 stand rejected under 35 U.S.C. §101.

However, in view of the above amendments, this ground of rejection is believed to be moot.

Claims 7 and 27 stand rejected under 35 U.S.C. §112, first paragraph.

However, in view of the above amendments, this ground of rejection is believed to be moot.

Claims 2, 7, 8, 11, 12, 15, 16, 22, 23, 27, 28, 31-37 and 40 stand rejected under 35 U.S.C. §112, second paragraph.

However, in view of the above amendments, this ground of rejection is believed to be moot.

Finally, Applicants are now in the process of reviewing relevant literature for definitions of the trade names used in the present specification and claims and will submit the same to the U.S. Patent Office as soon as the same are available.

Accordingly, in view of all of the above amendments and attendant remarks, it is believed that the present application now stands in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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